REMARKS

Applicants are re-submitting their previous after-final response, as requested by Examiner Coleman during a telephonic interview with the undersigned attorney on March 20, 2007, to permit the Examiner to enter the amendments to the claims as they reduce the issues on appeal.

Claims 1 to 56 are pending in this application and stand rejected. Applicants are herein amending claims 27, 33, and 55. Applicants request entry of the claim amendments and reconsideration of the rejections in light of the amendments and following remarks.

Summary of Rejections

Claims 1 to 56 stand rejected as follows:

- claims 1 to 56 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled;
- claims 25 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite;
- claims 1 to 26 stand rejected under 35 U.S.C. § 102(b) as allegedly lacking novelty over EP-A-0,778,023;
- claims 1 to 9 and 26 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 26 to 29 of US 10/969,715;
- claims 27 to 55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 11 to 28 of US 10/820,216;
- claims 27 to 56 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 to 95 and 104 to 108 of US 10/961,871; and
- claims 21 to 24 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 37 to 53 and 57 to 73 of US 10/267,159.

Claims 27 to 30 and 33 to 56 are *newly* rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants acknowledge with appreciation that the rejection of claims 25, 26, 33, 54, and 56 under 35 U.S.C. § 112, second paragraph, and the rejection of claims 1 to 26 under 35 U.S.C. § 102(b) as allegedly lacking novelty over Childers, *Drugs of the Future,* Baudy, *J. Med. Chem.,* Kinney, *J. Med. Chem.*, US-A-5,240,946, and US-A-5,168,103 have been withdrawn.

Amendments to Claims

Applicants are herein amending claims 27, 33, and 55 to correct obvious typographical errors:

- In claim 33, applicants are removing an extraneous hyphen in the name of the compound listed at e).
- In claims 27 and 55, applicants are correcting the carbon number in the alkylaryl moiety in R_6.

Applicants submit that no new matter is introduced by the amendments to the claims and that the amendments are fully supported by the specification, as originally filed, including the definition of alkylaryl provided in paragraphs **[0037]** and **[0039]** where the number of carbon atoms is 6 (from 1+5) to **21** (from 8+13):

> **[0037]** Aryl, as used herein, refers to an aromatic 5- to **13**-membered mono- or bi-carbocyclic ring such as phenyl or napthyl. Preferably, groups containing aryl moieties are monocyclic having 5 to 7 carbon atoms in the ring. Heteroaryl means an aromatic 5- to 13-membered carbon containing mono- or bi- cyclic ring having one to five heteroatoms which independently may be nitrogen, oxygen or sulfur. Preferably, groups containing heteroaryl moieties are monocyclic having 5 to 7 members in the ring where one to two of the ring members are selected independently from nitrogen, oxygen or sulfur. Groups containing aryl or heteroaryl moieties may optionally be substituted as defined below or unsubstituted.
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> **[0039]** Alkylaryl, as used herein refers to the group -R-Ar where Ar is aryl as defined above and R is an alkyl moiety having 1 to **8**, preferably 1 to 6, and more preferably 1 to 4 carbon atoms. Examples of alkylaryl groups include benzyl, phenethyl, 3-phenylpropyl, and 4-phenyl butyl.

> Alkylheteroaryl, as used herein refers to the group -R-hetAr where hetAr is heteroaryl as defined above and R is an alkyl moiety having 1 to 8, preferably 1 to 6, and more preferably 1 to 4 carbon atoms.

Applicants request the entry of the amendment under 37 C.F.R. § 1.116(b) because the amendments to the claims either cancel claims, comply with requirements of form expressly set forth in a previous Office Action, or present the rejected claims in better form for consideration on appeal.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1 to 56 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. More specifically, the Office maintains that it is not sufficient to support enablement of claims 1 to 56 by establishing a nexus between NMDA antagonists and the treatment of the diseases and/or disorders listed in the claims. The Office further urges that treatment does not imply prevention. Applicants traverse the rejection.

As previously explained, with respect to the prevention of disorders, no evidence has been presented that there is any reason to believe that a skilled artisan would doubt that the compounds of the invention would not be useful in preventing opiate tolerance, especially in light of the fact that NMDA receptor antagonists are known to prevent the opiate analgesia tolerance. See, for example, the Trujillo abstract (previously provided). Contrary to the allegations in the latest action, this abstract indicates that a decade of research establishes that "NMDA receptor antagonists have the ability to inhibit opiate tolerance," even if the exact mode of action is not known. Furthermore, medical professionals have means to measure tolerance to opiate analgesia and would have no difficulty administering the compounds of the invention to effect the desired result, *i.e.*, prevention of the tolerance. No other evidence has been presented that establishes that a skilled artisan would doubt the use of the compounds of the invention, which are NMDA receptor antagonists, would not be useful in the treatment of the listed diseases and conditions.

Applicants submit that the pharmaceutical composition claims meet the enablement requirements under 35 U.S.C. § 112, first paragraph. Applicants have described in sufficient detail to enable a person ordinary skilled in the art to make and use the intranasal compositions without undue experimentation. See, for example, applicants provide a description of the synthesis of the active compound on page 12, line 8 to page 14, line 3, three actual examples of how to formulate the intranasal compositions (Examples 1 to 3), and they also describe how other types of intranasal may be prepared on page 14, line 4 to page 19, line 8. Thus, applicants submit that the composition claims are enabled.

Further, applicants submit that the method of treatment claims also meet the enablement requirements under 35 U.S.C. § 112, first paragraph. With the exception of cerebral ischemia, it appears that the Office is challenging that there is a correlation between antagonists of the NMDA receptor and the treatment of the various diseases and conditions claimed. As applicants explained on page 14, line 8 to page 15, line 11, the present invention provides methods for treating conditions associated with glutamate abnormalities, *i.e.,* conditions produced by a disease or a disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor. The Office has provided no evidence that any of the listed conditions would not be expected to be treated by the compounds of the invention. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonably based upon the probative evidence. (citations omitted).

Applicant previously submitted a number of review articles that show that there is recognized correlation between antagonism at the NMDA receptors and the specified diseases and conditions set forth in the claims:

- Wood PL.
  The NMDA receptor complex: a long and winding road to therapeutics.

Drugs. 2005 Mar;8(3):229-35. Review.

- Heresco-Levy U.
  Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia.
  Expert Opin Emerg Drugs. 2005 Nov;10(4):827-44. Review.

- Bergink V, van Megen HJ, Westenberg HG.
  Glutamate and anxiety.
  Eur. Neuropsychopharmacol. 2004 May;14(3):175-83. Review.

- Parsons CG.
  NMDA receptors as targets for drug action in neuropathic pain.
  Eur J Pharmacol. 2001 Oct 19;429(1-3):71-8. Review.

- Brown DG, Krupp JJ.
  N-methyl-D-aspartate receptor (NMDA) antagonists as potential pain therapeutics.
  Curr Top Med Chem. 2006;6(8):749-70

- McCulloch J.
  Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man.
  Br J Clin Pharmacol. 1992 Aug;34(2):106-14. Review.

Applicants have demonstrated that compounds useful in the intranasal compositions of the invention, NMDA receptor antagonists through testing in the art-recognized *in vivo* prostaglandin E_2-induced thermal hypersensitivity test. If the prior art is such a particular model is recognized as correlating to a specific condition, then it should be accepted by the Office as correlating unless the Office has evidence that the model does not correlate. Even with such evidence, the Office must weight the evidence for and against such correlation and determine whether a skilled artisan would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). The Office has not met this burden.

Accordingly, applicants submit that claims 1 to 56 meet the enablement requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 25 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 27 to 30 and 33 to 56 are *newly* rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants acknowledge with appreciation that the rejections of claims 26, 33, and 56 under 35 U.S.C. § 112, second paragraph, have been withdrawn. Applicants traverse the remaining indefiniteness rejections.

Claims 25 and 54

Claims 25 and 54 stand rejected for using the phrase "pain relieving agent." Applicants traverse the rejection because a skilled artisan would have no difficulty understanding the meaning of the phrase. Furthermore, on page 23, lines 22 to 25 and page 24, lines 10 to 25, applicants have provided numerous specific examples of pain relieving agents, leaving no doubt with the skilled artisan to the metes and bounds of the invention with respect to the pain relieving agents.

Claims 27 to 30 and 33 to 56

Claims 27 to 30 and 33 to 56 are *newly* rejected for ambiguity with respect to the alkylaryl group in R_6 (a ~~C_6 to C_2~~ C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety). Applicants are herein amending claims 27 and 55 to correct the typographical error with respect to the alkylaryl group in R_6. Applicants submit that the amendment to claims 27 and 55 renders moot the rejection of claims 27 to 30 and 33 to 56. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claims 27 and 55

Claims 27 and 55 are *newly* rejected for allegedly lacking antecedent basis for the limitation "5 to 13 carbon atoms in the aryl moiety" in R_6. Applicants are herein amending claims 27 and 55 to correct the typographical error with respect to the alkylaryl group in R_6. Applicants submit that the amendment to claims 27 and 55 renders moot the rejection of the claims If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claim 33

Claim 33 is *newly* rejected as allegedly ambiguous with respect to species e). Applicants are herein amending claim 33 to correct the typographical error with respect to the extraneous hyphen in the name of the compound. Applicants submit that the amendment to claim 33 renders moot the rejection of the claim. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Applicants submit that claims 25, 27 to 30, and 33 to 56, as amended, meet the definiteness requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

Claims 1 to 26 stand rejected under 35 U.S.C. § 102(b) as allegedly lacking novelty over EP-A-0,778,023. Applicants traverse the rejection. The remaining novelty rejections have been withdrawn.

Composition claims 1 to 9 require an excipient for intranasal administration and method claims 10 to 26 require that the composition of claim 1 be administered intranasally. It is the Office's position that because EP-B1-0,778,023 discloses that rapamycin may be administered intranasally in **[0029]** and also discloses that the product contains an NMDA antagonist such as [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl] phosphonic acid (EAA-090), it necessarily discloses that the EAA-090 is administered intranasally thereby anticipating claims 1 to 26. Applicants disagree because EP-B1-0,778,023 never discloses a product containing both rapamycin and EAA-090 that is administered intranasally.

While EP-B1-0,778,023 discloses that the rapamycin may be administered intranasally, it further indicates that the NMDA antagonist does not necessarily need to administered at the same time. See **[0008]**. Even if the rapamycin and the NMDA antagonist are administered at the same time, this does not necessarily require that the compounds administered in the same manner. Importantly, EP-B1-0,778,023 is silent with respect to intranasal administration or compositions of the NMDA antagonists and is not inherent in the disclosure. The missing descriptive matter is not necessarily present in the thing described in the reference. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)(quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981); *Ex parte Skinner*, 2 USPQ 2d 1788, 1789 (B.P.A.I. 1986). (*See also* M.P.E.P. §2112 (IV)). The inherent feature must *necessarily* lead one skilled in the art to the claimed subject matter. *Hyatt v. Boone*, 146 F.3d 1348, 47 USPQ.2d 1128 (Fed. Cir. 1998). *Kennecott Corporation v. Kyocera International, Inc. and Kyoto Ceramic Co., Ltd.*, 835 F.2d 1419, 5 USPQ.2d 1194 (Fed. Cir. 1987). The fact that intranasal administration of both the rapamycin and EAA-090 might have been carried out is insufficient.

Since EP-B1-0,778,023 does not disclose each and every element of the claim either explicitly or inherently, EP-B1-0,778,023 does not anticipate claims 1 to 56. Accordingly,

applicants request withdrawal of the rejection under 35 U.S.C. § 102(b) over EP-B1-0,778,023.

Obviousness-type Double Patenting Rejections

Claims 1 to 9 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 26 to 29 of US 10/969,715. Claims 27 to 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 11 to 28 of US 10/820,216. Claims 27 to 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 to 95 and 104 to 108 of US 10/961,871. Finally, claims 21 to 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 37 to 53 and 57 to 73 of US 10/267,159.

Applicants request that these provisional rejections be held in abeyance until the identification of otherwise allowable subject matter.

Conclusions

Applicants request:

(1) entry of the amendments to the claims;

(2) reconsideration and withdrawal of the rejections of the claims;

(3) reconsideration and withdrawal of the finality of the rejection of the claims; and

(4) allowance of claims 1 to 56.

If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (404) 459-5642.

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